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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

ART UNIT	PAPER NUMBER
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/358,937

Applicant(s)

SPRADLING ET AL.

Examiner

Joseph Woitach

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office within three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 14 August 2001.
- 2a) ☐ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) 3, 11-15, 17, 19-22, 32 and 34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1, 2, 4-10, 12, 13, 16, 18, 20-21, 23-31, 33, 35 and 36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are objected to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not state that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrections are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the priority documents have been received in this National Stage application in the International Bureau (PCT Rule 17.2(a)).
* See the attached declaration and Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-89)
- 2) ☐ Notice of Draft Person's Examination Review (PTO-948)
- 3) ☐ Information Disclosure Statement (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

This application is an original application filed July 23, 1999 which claims benefit to provisional application 60/094,008, filed July 24, 1998.

Applicants amendment filed August 14, 2001, paper number 14 has been received and entered. Claim 2 has been amended. Claims 1-36 are pending, claims 3, 11-15, 17, 19-22, 32 and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, and claims 1, 2, 4-10, 16, 18, 23-31, 33, 35 and 36 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-10, 16, 18, 23-31, 33, 35 and 36 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is vague and unclear in the recitation 'stimulating signal transduction by a bone morphogenetic protein (BMP) signaling pathway in at least one cell of said population'.

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Applicants argue that the specification teaches that the germline cells can be stimulated directly or indirectly through other cells in a mixed population, and thus both are within the scope of the claim. In addition, Applicants point out that the stimulation of the BMP pathway can result in an increase number of germline cells, however this is not necessarily an increase in proliferation rather could be due to an increased maintenance. See Applicants amendment, page 2. Applicants argument have been fully considered and have been found persuasive in part.

First, the instant specification and the art of record teaches the requirement of the BMP related pathways for oogenesis in the fly, and the final effect measured in experiments studying the effect of BMP and related molecules is the number of germline cells. Examiner agrees that it is not clear if the increased number of germline cells results from an increased proliferation or an increased maintenance. Thus, this portion of the rejection of claim 1 is withdrawn. Secondly, the specification and the art of record teaches that it is the stimulation of the BMP pathway in the germline cells which increases the number of germline cells, not the stimulation of other cells. Examiner would agree that the stimulation of the germline can be direct or indirect, however because step (b) uses a mixed population of cells, the methods should be directed to stimulating the germline cells in the population. It is unclear if the method is directed to stimulating the pathway in the germline stem cell directly or stimulating another cell in the population which in turn results in the maintenance of the germline stem cells. If it is the latter situation, then the claim contains a cell population that is not clearly defined. If the BMP pathway in the germline cell is not affected, rather the BMP pathway of a secondary cell in the population, the claim

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should clearly indicate this essential cell in the mixed population necessary and capable of supporting the maintenance of germline cells. It is noted that Applicants have elected species 3(b) directed to *in vivo* methods and species 4(c)(i) directed to the transduction with a nucleic acid and further Dpp, (see previous office action page 1). Though the claims do not specifically recite these limitations, the examination of the claims are limited to the elected invention, and if allowed would be limited by estoppel to these elected embodiments. It is suggested that the claims be amended to more clearly reflect the elected invention

Claim 7 is vague, unclear and indefinite in the recitation of 'stimulated by providing at least 10% more Decapentaplegic (Dpp) activity'. Applicants argue that Dpp activity can be determined and the increase in activity be confirmed. Applicants state that mutant alleles of Dpp and their activities are known in the art. See Applicants amendment, page 3. Applicants arguments have been fully considered but not found persuasive.

As noted in the previous office action, the type of activity of the Dpp is not defined, and it is known in the art that BMP is a large family of molecules which has different effects on different cells, so different activities depend both on the cell affected and the specific BMP used. In addition, there are many forms of Dpp (for example, dpp^{c90} , dpp^{hr4} , dpp^{hr56} specification; Table 1 and art of record) and it is unclear if recitation of 'Dpp' encompass these alternative forms of the wild type Dpp or only the wild type Dpp. Applicants arguments are unpersuasive because while the mutant alleles are known in the art, there is no indication of their absolute activity for

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use in the claimed method. Applicants state that the activities can be tested, however this suggests that the activities are then in fact not known and the artisan is left to determine the potential usefulness of the various forms of Dpp, and if useful, the amount and means to deliver the correct amount of Dpp to achieve at least an increase of 10% activity. In addition, in view of Applicants arguments above regarding claim 1, and the indirect effect on a mixed population of cells for maintenance of germline cells, the specification is silent to what the indirect effect would be or how this could or would be measured. The claim is vague and unclear on how the artisan would achieve the limitation of an increase in 10% activity.

Further, Applicants argue that the BMP pathway is a well studied pathway. However, as noted in the previous action and highlighted by Applicants present arguments, it is unclear what is encompassed by the BMP signaling pathway because the effect can be direct and indirect, and thus, while the components of the BMP have been fairly defined in the art, the claims encompass changes and stimulating effects beyond just the BMP pathway. Further, the types of possible mutations is subject to open language and encompasses more than mutating dpp, and therefore, what is encompassed as being stimulated is unclear and indefinite.

Claim 10 recites a Dpp protein, BMP-2 and BMP-4, however the elected invention is drawn to the delivery of a nucleic acid encoding Dpp. Applicants have elected the species of Dpp, and the invention currently under examination does not include providing BMP-2 or BMP-4. Further, the invention is directed to delivering a polynucleotide and does not encompass the

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delivery of Dpp protein. Deleting BMP species and more clearly indicating that the Dpp protein is encoded by a polynucleotide may obviate the basis of the rejection.

Claim 26 is unclear and confusing because the method of claim 1 is for the maintenance of germline stem cells. Applicants argue that this is a well established property of germline cells and the maintenance of this property is consistent with the practice of the claimed method. See Applicants amendment, page 3. Applicants arguments have been fully considered but not found persuasive.

As noted in the previous office action, claim 26 encompasses differentiation of the cell and not maintenance. Examiner agrees that a germline cell is capable of differentiating, however the instantly elected and claimed method is directed to maintaining germline stem cells. First, the method of differentiating cells is beyond the scope of the elected invention. Secondly, it is unclear how differentiating the cells would accomplish the intended preamble recited in independent claim 1. Once the cells are differentiated, the cells are no longer germline cells and thus, the preamble of claim 1 is not affected. If Applicants intend to more clearly indicate the inherent properties of the germline cells maintained by practicing the method of claims 1 and 25, the claims should be amended to more clearly indicate this effect, absent an active step of actually differentiating the germline cells.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-10, 16, 18, 23, 24, 28-31, 33, 35 and 36 stand rejected under 35 U.S.C. 102(b) as being anticipated by Twombly *et al.*

Applicants point out that anticipation requires 'each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior reference' citing *Verdegall Bros v. Union Oil Co. of Calif* and *Richardson v. Suzuki Motor Co.*, and argue that Twombly *et al.* do not teach the claimed invention. Specifically, Applicants state that Twombly *et al.* disclose that TGF- β signaling must be transmitted from the soma to the germline during oogenesis (Twombly *et al.*, page 1556), however an oocyte is not a germline stem cell and thus merely discloses that TGF- β affects the development of oocytes (Applicants amendment, top of page 4). Applicants arguments have been fully considered but not found persuasive.

Twombly *et al.* teach a transgenic *Drosophila* wherein the transgene expressed is Dpp, a TGF- β homolog (page 1556; second column). As noted in Applicants' arguments, Twombly *et al.* summarize previous experiments stating that dpp is not required during oogenesis (Irish and Gilbert) rather, that it's signal and signal pathway is required by the germline stem cells (page

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1556; middle of first column). Further, experiments in which the sax receptor is knocked-out in germline cells clearly indicates the need for dpp signaling in the germline stem cells (page 1561; first and second column in bridging paragraphs) and is generally supported the experiments set forth in Examples 3 and 4 of the instant specification. As in the instant specification, Twombly *et al.* use structural changes in the fly, such as the final production of oocytes, as a measurement of effect of germline cells. Though Twombly *et al.* do not specifically examine the pluripotent or totipotent state of the germline stem cells, the evidence provided in Twombly *et al.* clearly indicated that the method of providing dpp to germline cells would inherently result in the increased maintenance of the germline stem cells. It is noted that, where, as here, the claimed and prior art products are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. *In re Ludtke*. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In the instant case, the evidence of record present in Twombly *et al.* clearly indicates that the expression of *dpp* would result in affecting the germline cells of the fly. In view of the teachings of the instant specification as evidenced in the working examples, the method of providing dpp in a transgenic fly as taught by Twombly *et al.* clearly anticipates the claimed invention. Finally,

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Twombly *et al.* teach the expression and disruption of the sax gene as well as the use of FLP and various alternate forms of dpp (page 1556; materials and methods section). Thus, the claimed invention is anticipated, and therefore, the rejection is maintained.

Claims 1, 2, 4-10, 16, 18, 23, 24, 28-31, 33, 35 and 36 stand rejected under 35 U.S.C. 102(b) as being anticipated by Forbes *et al.*

Applicants argue that the ectopic expression of dpp in the ovary of the fly as taught by Forbes *et al.* does not demonstrate that germline stem cells are maintained. Rather, it is stated that Forbes *et al.* teaches the fusion of egg chambers containing germ-line cysts. See Applicants amendment, pages 4-5. Applicants' arguments have been fully considered, but not found persuasive.

As in Twombly *et al.*, Forbes *et al.* teach the ectopic expression of Dpp in *Drosophila* through the expression of a transgene and observe that expression of Dpp results in a multiplicity of germline cells in the ovary (page 3291; first and second column bridging paragraph and figure 7). Normally the germarium of the fly has three recognizable regions, wherein region contains 2-3 germline stem cells (reviewed in the introduction, page 3284). The egg chamber structures containing 16 germ line cells clearly indicates that the expression of dpp has an effect on the germline cells. As note in Applicants arguments regarding 35 USC 112, second paragraph, rejection, the maintenance of the germline cell may result in an increased number of cells or just maintain the cells. In the instant case, the ectopic expression of dpp and the increased number of

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germline cells observed clearly teaches the limitations of the instantly claimed invention are taught by Forbes *et al.* Finally, Forbes *et al.* teach the expression of several other transgenes such as hh, en, and wg (page 3284; material and methods), and the ptc gene is disrupted resulting in the lack of activity of said gene (page 3285; bottom of first column). Thus, the claimed invention is anticipated by the teachings of Forbes *et al.*, and therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1 and 25-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over either Forbes *et al.* or Twombly *et al.* and Lin *et al.*

Applicants argue that Forbes *et al.* and Twombly *et al.* do not anticipate the claims as argued above, and the teachings of Lin *et al.* for the transplantation of stem cells into a host *Drosophila* do not remedy this deficiency. See Applicants amendment, page 5. Applicants' arguments have been fully considered but not found persuasive.

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Applicants' arguments are not persuasive because Forbes *et al.* or Twombly *et al.* each teach a method wherein Dpp is expressed as a transgene in *Drosophila* resulting either inherently or as observed by Forbes *et al.* in the increase in germline stem cells. Further, each reference teaches the additional expression and disruption of genes in the *Drosophila* genome. However, neither reference teaches the transfer of germline stem cells into a host *Drosophila*. Lin *et al.* teach the transfer of germline stem cells into a host *Drosophila* for the study of germarial cells (entire reference; summarized in the abstract). Thus, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the claimed invention to use the methods of germarial cell transfer as taught by Lin *et al.* to implant the stimulated germline stem cells as taught by Forbes *et al.* and Twombly *et al.* One would have been motivated to transfer these cells to examine the influence of transgene behavior on oogenesis or other parts of development as Lin *et al.* did for various strains/genotypes of donor and host *Drosophila*. There would have been an reasonable expectation of success given the results of Lin *et al.* with the multiple different strains of *Drosophila* to transfer stimulated germline stem cells as taught in Forbes *et al.* and Twombly *et al.* for the further study of germarial development.

Thus, the claimed invention is *prima facie* obvious, and therefore, the rejection is maintained.

Conclusion

No claim is allowed.

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THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is (703)308-4724.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

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Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800 16.30

Joseph T. Weitach